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TREATMENT OF PYOGENIC MENINGITIS IN INFANTS AND CHILDREN*

Sidney Ross, M.D.

In this discussion, I shall attempt to cover some of the newer concepts in the treatment of pyogenic meningitis and delineate in some detail the more recent advances in the over-all management of this disease.

By the way of prologue, I might say that my remarks will be chiefly pertinent to the pediatric age group since my experience with the disease has been derived primarily from infants and children. Secondly, my comments will be directed only against pyogenic meningitis and will exclude any reference to meningitis of tuberculous etiology.

IS INTRATHECAL THERAPY NECESSARY

The necessity of intrathecal therapy in the treatment of meningitis has been questioned during the past two or three years. Formerly, it was common to resort to the intrathecal route as an indispensable adjunct in the treatment of this disease. However, it is now generally conceded that it is preferable to avoid the administration of drugs into the subarachnoid space especially when one can accomplish the same result by using either the oral or parenteral routes.[1, 2] We are indebted to one of the members of this panel, Doctor Dowling, for demonstrating that massive doses of penicillin, i.e., 1 million units every two or three hours intramuscularly, will penetrate the blood-brain barrier and result in an adequate level of penicillin in the spinal fluid.[3] Some other drugs used in the treatment of meningitis also penetrate this barrier adequately. Sulfadiazine will produce spinal fluid levels ranging from 35 to 50 per cent of the coexisting blood sulfa level. Similarly, chloramphenicol crosses the bloood-brain barrier not unlike the sulfa drugs.[4] With the other broad-spectrum antibiotics, however, we run into a somewhat different problem. It has been shown that the tetracyclines penetrate the barrier less adequately than do either the sulfonamides or chloramphenicol,[5] although there is a preliminary indication that tetracycline penetrates this barrier to a greater degree than either oxytetracycline or chlortetracycline.[6] It has been our general experience that adequate therapeutic results can be obtained in pyogenic meningitis when the tetracyclines are employed either orally or parenterally without resorting to intrathecal administration. With the drugs currently available for the efficient treatment of meningitis, systemic therapy will suffice, precluding the necessity of intrathecal administration.

* Presented before the International Symposium on Antibiotics sponsored by Lederle Laboratories, New York City, November 2, 1954. Reprinted from Antibiotics and Chemotherapy (April 1955) with permission from Dr. Henry Welch.

CURRENT STATUS OF ANTISERUM IN MENINGITIS THERAPY

Appraising antiserum in the current treatment of pyogenic meningitis, I think it can be safely said that this is of only historical importance today. Certainly in meningococcic meningitis, antiserum has been completely disavowed. Similarly it is becoming increasingly apparent that *Hemophilus influenzae* meningitis rabbit antiserum has been rendered superfluous by the broad-spectrum antibiotics.[7] We have not employed rabbit antiserum in the treatment of *H. influenzae* meningitis for the past four years; as the broad-spectrum antibiotics were used during this time, our results have been extraordinarily good.

One might be justified in concluding that antiserum is no longer necessary in the management of any type of pyogenic meningitis.

ANTAGONISM BETWEEN DRUGS COMMONLY USED IN THE TREATMENT OF PYOGENIC MENINGITIS

Since one frequently employs combination therapy in the treatment of pyogenic meningitis, the question arises whether antagonism between antimicrobial agents may be significant. The experimental observations of Jawetz[8, 9] indicate that chlortetracycline, oxytetracycline, and chloramphenicol are at times capable of interfering with the action of both streptomycin and penicillin. Lepper and Dowling[10] have added a clinical counterpart to these experimental observations in their report of 14 patients with pneumococcal meningitis treated with both penicillin and chlortetracycline of whom 11 died, whereas, in a control group treated with penicillin alone, only three cases ended fatally. But there is little additional clinical evidence to support Jawetz's experimental observations on antagonism. Ahern and Kirby[11] treated 25 cases of pneumococcal pneumonia with a combination of chlortetracycline and penicillin and observed much the same clinical response as in a comparable control group of 25 patients treated with penicillin alone. Our own experience coincides with that of Ahern and Kirby. We have frequently used combinations of penicillin with one of the broad-spectrum antibiotics and have not been able to detect any clinical indication of antagonism. From the clinical evidence thus far, one should have no compunction in the simultaneous use of penicillin and one of the broad-spectrum antibiotics in the treatment of pyogenic meningitis.

THE PROBLEM OF RESISTANCE IN ORGANISMS CAUSING MENINGITIS

The question of resistance of organisms causing meningitis has become a more pressing problem within the recent past. It has been known for some time that mutant stains of *H. influenzae* can rapidly become resistant to streptomycin.[12] Similarly some of the coliform organisms, which fortunately are rare as causative agents in pyogenic meningitis, have also shown a sharp

increase in the number of strains resistant to streptomycin. These considerations make streptomycin a less desirable and less useful drug in meningitis therapy, especially since the advent of broad-spectrum antibiotics.

With regard to sulfonamide drugs, there is some indication that a moderate number of strains of *H. influenzae* have become resistant to sulfadiazine.[13] As for meningococci, streptococci, and pneumococci, there is no substantial evidence that these three organisms have become more resistant to sulfonamides during the past several years.

The increasing number of penicillin-resistant strains, together with the increasing number of strains resistant to the tetracyclines, make the problem of adequate management of staphylococcal meningitis an imposing one.[14] Fortunately only a few strains of Staphylococcus aureus are resistant to erythromycin and chloramphenicol and, equally fortunately, staphylococcal meningitis is relatively rare at the present time.

As for the broad-spectrum antibiotics, one can make the general statement that, with the notable exceptions of Staphylococcus aureus and some of the coliform organisms, there has been no definitive increase in the number of resistant strains of organisms which commonly cause pyogenic meningitis.

SUBDURAL EFFUSION AS A COMPLICATION OF PYOGENIC MENINGITIS

McKay et al[15] in 1950 were the first to describe collections of subdural fluid in infants convalescing from *H. influenzae* meningitis. Since then, there have been several additional reports indicating the frequency of this complication. For example, Smith et al[16] reported subdural effusions in 20 of 43 children with pyogenic meningitis.

It is well to point out that subdural effusions may occur as a complicating feature irrespective of the etiologic organism. We have seen them following meningitis due to *H. influenzae*, Meningococcus, Pneumococcus, and Staphylococcus as well as other pyogens. Recently we treated a child with typhoid meningitis who developed a subdural effusion.

How does one make a diagnosis of subdural effusion complicating meningitis? McKay et al[15] have suggested that subdural taps be performed on any child with meningitis whose temperature had not defervesced in 48 hours, whose spinal fluid was not sterile after 48 hours of therapy, or who had focal convulsions or gross neurologic abnormalities during the convalescent phase.

However, I should like to broaden this recommendation by proposing that any infant with pyogenic meningitis who has an open fontanelle should have the benefit of a subdural tap irrespective of the course of the disease. This recommendation is based on the fact that we have seen several in-

stances where a child was ostensibly doing well and presented none of McKay's criteria suggesting a subdural collection of fluid; yet when a routine subdural tap was performed, substantial quantities of fluid were obtained. In our opinion, a subdural effusion following meningitis may present suggestive symptoms or may be completely occult; hence the blanket recommendation for a routine subdural tap wherever the anterior fontanelle is open.

It might be added that the performance of subdural taps is extremely simple and hardly requires the services of a neurosurgeon. All the members of our resident pediatric staff are taught to perform subdural taps and, if a modicum of care is exercised, the procedure can be done more easily than a spinal tap. Subdural taps are performed by inserting the needle perpendicular to the skull at the extreme lateral margin of the anterior fontanelle. The needle should not be advanced more than one fourth of an inch and the position of the needle should not be altered or the direction changed in an attempt to obtain fluid. The fluid is usually blood tinged or xanthochromic and generally has a high protein content ranging from 200 to 1,500 mg. per cent. It is always advisable to perform a subdural tap bilaterally and it is further recommended to perform two or perhaps even three taps at two day intervals when the initial tap was negative, inasmuch as the effusion may appear late in convalescence.

In the treatment of subdural effusions complicating pyogenic meningitis, it has been our general practice to adopt a conservative approach for the first 10 to 14 days, resorting to repeated taps every second day in an attempt to "dry up" the subdural space. Approximately 10 to 15 cc. of fluid is drawn off each time. If the amount of fluid becomes progressively less with each subdural tap and there are no neurologic sequellae, fever, irritability, or focalizing signs, then no neurosurgical intervention is recommended. But if abundant quantities of xanthochromic fluid with high protein content remain in the subdural space in spite of repeated subdural taps, burr holes are performed and, if a well developed membrane is found, a craniotomy is done and the membrane removed.

The rationale for removing the thickened subdural membrane lies in the fact that the latter may act as a constricting envelope which could very well prevent normal brain growth. In addition, the resulting cicatrix could act as a potential epileptogenic focus.

In our experience, electroencephalogram tracings have proved of little or no value as indices of the presence or absence of a subdural effusion following meningitis.

During the past three years, we have found subdural effusions complicating pyogenic meningitis in 21 out of 46 children whose anterior fontanelles were open. It is difficult to say how frequently this complication

occurs in children whose fontanelles are closed since one would be loath to recommend the routine performance of burr holes in older children unless some overt neurologic stigmata were in evidence.

EVALUATION OF DRUGS AVAILABLE FOR MENINGITIS THERAPY

Here is a brief outline of the virtues and drawbacks of the drugs currently available for the treatment of pyogenic meningitis.

I. Sulfonamides

Advantages:

1. Wide antibacterial spectral range.
2. Inexpensive
3. Easily administered intravenously and orally.
4. Crosses blood-brain barrier readily.

Disadvantages:

1. Occasional toxicity.
2. Laboratory work (hemograms, urines, sulfa levels).
3. Sulfa-resistant strains, i.e., *H. influenzae* and coliform organisms.

II. Penicillin

Advantages:

1. Lack of toxicity.
2. Very effective against Pneumococcus and Streptococcus.
3. Useful against Meningococcus.

Disadvantages:

1. Crosses blood-brain barrier poorly except where massive intramuscular doses are employed.
2. Limited antimicrobial spectral range. Ineffective against *H. influenzae*, coliform organisms, and some strains of Staph. aureus.

III. Streptomycin

Advantages:

1. Effective against gram-negative organisms, i.e., *H. influenzae* and some coliform organisms.

Disadvantages:

1. Toxic effects, eighth nerve involvement.
2. Rapid development of resistant strains.
3. Crosses blood-brain barrier poorly.
4. Limited antimicrobial spectral range, i.e., ineffective against coccal organisms.

IV. Chloramphenicol

Advantages:

1. Wide antibacterial spectral range. Very effective against *H. influenzae*. Also effective against Staph. aureus, Streptococcus, Pneumococcus, Meningococcus, and many coliform organisms.

2. Crosses blood-brain barrier well.
3. Easily administered intravenously, intramuscularly, and orally.

Disadvantages:

1. Toxicity. Bone marrow depressant in rare idiosyncratic individual.

V. Tetracyclines (oxytetracycline, chlortetracycline, and tetracycline)

Advantages:

1. Wide antibacterial spectral range, i.e., *H. influenzae*, Meningococcus, Pneumococcus, Streptococcus, Staphylococcus, and coliform organisms.
2. Easily administered intravenously, intramuscularly, and orally.

Disadvantages:

1. Limited passage across blood-brain barrier (except tetracycline).
2. Increasing number of Staph. aureus strains resistant to tetracyclines.

SUGGESTED MANAGEMENT OF VARIOUS TYPES OF PYOGENIC MENINGITIS

I will outline briefly the type of therapy which one would recommend in the various types of pyogenic meningitis encountered in the pediatric age group. It is well to bear in mind that with the plethora of drugs currently available, several different modalities of therapy are possible. The effective drugs are here enumerated and followed by a suggested mode of management, due regard being paid to possible alternatives.

1. H. influenzae meningitis

Effective drugs include sulfadiazine, chlortetracycline, oxytetracycline, tetracycline, chloramphenicol, and streptomycin.

Treatment of choice: Chloramphenicol most effective agent against *H. influenzae* meningitis. May be used alone or in combination with sulfonamides. Give chloramphenicol parenterally in doses of 50 mg. per pound per 24 hours initially and resume oral chloramphenicol when feasible. Therapy should be continued for 10 days after temperature is normal and spinal fluid sterile. When sulfonamides also employed, give 2 to 3 grains per pound per 24 hours; maintain sulfa level between 10 to 15 mg. per cent. Chlortetracycline, oxytetracycline, and tetracycline have also been used successfully. *H. influenzae* rabbit antiserum not necessary. Streptomycin, formerly the drug of choice, is no longer indicated since the advent of broad-spectrum antibiotics. Can currently anticipate 90 to 95 per cent recovery.

2. Meningococcal meningitis

Effective agents include sulfadiazine, penicillin, chloramphenicol, oxytetracycline, chlortetracycline, and tetracycline.

Treatment of choice: Excellent results with sulfadiazine alone, with 95 per cent recovery. Give 2 to 3 grains per pound per 24 hours and continue for seven days after temperature normal and spinal fluid sterile. Penicillin as supplementary therapy may be used in cases responding poorly to sulfadiazine. Broad-spectrum antibiotics very effective also.

3. Pneumococcal meningitis

Effective agents include penicillin, sulfadiazine, chloramphenicol, oxytetracycline, chlortetracycline, tetracycline, and erythromycin.

Treatment of choice: Combination of sulfadiazine and penicillin excellent therapy. Give crystalline penicillin, 1 million units every three hours intramuscularly, and sulfadiazine, 2 to 3 grains per pound per 24 hours. After three days, procaine aqueous penicillin (600,000 units every eight hours intramuscularly) may be substituted for crystalline penicillin. No intrathecal penicillin necessary. Continue combined therapy until both temperature normal and spinal fluid sterile for 10 days. Broad-spectrum antibiotics may also be used successfully. May expect 80 to 90 per cent recovery if treated early and energetically.

4. Staphylococcal meningitis

Effective drugs include penicillin, sulfadiazine, erythromycin, chloramphenicol, oxytetracycline, chlortetracycline, and tetracycline.

Treatment of choice: Sensitivity of organism should be determined promptly in view of increasing number of strains of Staphylococcus aureus resistant to penicillin and the tetracyclines. If organism sensitive, give 1 million units of crystalline penicillin intramuscularly every three hours for three days; then switch to procaine aqueous penicillin (600,000 units every eight hours intramuscularly for 10 to 14 days). May also use one of the broad-spectrum antibiotics concomitantly. If organism is only moderately sensitive or resisant, a combination of erythromycin (20 mg. per pound per 24 hours) and chloramphenicol (50 mg. per pound per 24 hours) is recommended.

5. Streptococcal meningitis

Effective drugs include penicillin, sulfadiazine, erythromycin, chloramphenicol, oxytetracycline, chlortetracycline, and tetracycline.

Treatment of choice: Same as for pneumococcal meningitis.

6. Meningitis due to gram-negative bacilli: (including Escherichia coli, Pseudomonas, paracolon, Proteus, and Aerobacter aerogenes)

Effective drugs include chloramphenicol, chlortetracycline, oxytetracycline, tetracycline, sulfonamides, streptomycin, and polymyxin B.

Treatment of choice: Sensitivity of coliform organisms should be deter-

mined promptly in view of great variability of strain resistance. Coliform organisms generally sensitive to broad-spectrum antibiotics. Proteus and Pseudomonas difficult to treat effectively. Polymyxin B may be useful in Pseudomonas meningitis. Each case of coliform meningitis to be treated according to sensitivity of organism.

WATERHOUSE-FRIDERICHSEN SYNDROME

Until recently, the prognosis in the Waterhouse-Friderichsen syndrome was uniformly fatal; however, with the advent of the corticoids, the outlook has currently improved to some degree although the entity is still a most formidable one and requires extremely vigorous therapy. During the past two years, we have treated five cases of acute adrenal insufficiency secondary to fulminating meningococcemia, with three recoveries and two deaths.

Because of the importance of gravity of this disease and in view of the more hopeful prognosis when intensive therapy is initiated promptly, I would like to suggest the following outline of management.

I. Laboratory work-up
   A. Spinal tap
      (1) Immediately on admission.
      (2) Daily thereafter for three days if positive; then every third day until discharge.
      (3) At least one repeat tap if admission tap negative.
   B. Blood culture
      (1) Immediately on admission.
      (2) Daily thereafter for three days.
   C. Nasopharyngeal culture
      Immediately on admission.
   D. Petechial smear
      Immediately on admission.
   E. Blood chemistries
      (1) Blood urea nitrogen, blood sugar, CO_2, chlorides, sodium, potassium.
      (2) Immediately on admission and daily thereafter for three days.
   F. Hematocrit and blood type and cross match.
      Immediately on admission.
   G. Complete blood count and urine
      (1) Immediately on admission.
      (2) Daily thereafter for three days.
      (3) Every three days until discharge.
   H. Total circulating eosinophil count
      (1) Immediately on admission.

(2) Every two hours for the first 12 hours.
(3) Then every two days.

I. Thorne test (with ACTH)—fifth, tenth, and fifteenth day.
J. Electrocardiogram daily as indicated.
K. Blood sulfa level daily.

II. Clinical observations
A. Temperature, pulse, and respirations every two hours during the first 12 hours; then every four hours thereafter.
B. Blood pressure
(1) Every hour during the first 12 or 24 hours.
(2) Then every two hours during the next 24 hours as indicated.
(3) Then every four hours as long as necessary.
C. Observe for congestive failure
(1) Enlargement of the liver.
(2) Dyspnea
(3) Heart rate
(4) Rales at lung bases.
(5) Roentgen-ray of the heart (portable).
(6) Edema.

III. Treatment
A. Continuous oxygen
B. Continuous intravenous immediately on admission
(1) Blood transfusion immediately.
(2) Adequate amounts of saline.
(3) Glucose with Hartman's solution.
C. Antibiotic therapy
(1) Tetracycline intravenously 10 mg./Kg. every six hours.
(2) Sodium sulfadiazine intravenously 100 mg./Kg. every six hours.
(3) Penicillin (aqueous crystalline) 1,000,000 u. stat intramuscularly and every two hours for two or three days. Then procaine aqueous penicillin 600,000 u. intramuscularly every 12 hours.
D. Cortisone
(1) 50 mg. immediately intravenously (intravenous preparation only) and 50 mg. immediately intramuscularly.
(2) Then 25 mg. intramuscularly every 12 hours for two days.
(3) Then 25 mg. orally every 12 hours for two days.
E. Adrenal cortical extract
25 to 50 cc. immediately intravenously.
F. Norepinephrine
If needed for blood pressure maintenance.

THE CONTINUING IMPORTANCE OF EARLY DIAGNOSIS OF MENINGITIS

An extremely important point which determines the results one will achieve in meningitis is the problem of early diagnosis and prompt initiation of treatment. One can speak glibly of diagnosing meningitis early, but it should be borne in mind that such a diagnosis in the pediatric age group poses problems more complex than in adults. In the average adult and older child, one observes various manifestations of meningeal irritation early, whereas in infants overt evidence of meningeal irritation, such as nuchal rigidity and positive Kernig and Brudzinski signs, are much less reliable diagnostically. One of the more significant findings in infants is the presence of a bulging anterior fontanelle, although this is not always present. We have seen a moderate number of cases at Children's Hospital where the resident physician, acting merely on a hunch or because he could not explain a cryptogenic fever, performed a spinal tap and found cloudy fluid.

In view of the variations in signs and symptoms of meningitis in the infant age group, the importance of performing lumbar punctures where doubt exists cannot be stressed too strongly. This is based on the fact that early manifestations of meningitis in infants are often nonspecific, consisting only of fever, fretfulness, vomiting, and occasionally convulsions. When more overt clinical manifestations of meningeal irritation become apparent the disease is often well advanced. It is the practice at Children's Hospital to perform routinely a lumbar puncture on every child admitted to the hospital with fever and convulsions. Early diagnosis and prompt initiation of therapy determine, in no small part, the results of treatment. If we temporize too long in making a diagnosis, we may be left with a "recovery," but also with a severely damaged child.

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TREATMENT OF ACQUEDUCTAL STENOSIS FOLLOWING ENCEPHALITIS WITH VENTRICULO-CISTERNAL SHUNT

Arthur A. Morris, M.D., F.I.C.S., F.A.C.S.

Case Report

On December 7, 1949, this four year old child was first admitted to Children's Hospital by Dr. George Maksim and was treated for encephalitis and discharged February 12, 1950. On discharge from the hospital he could not walk and required extensive training. However, he made satisfactory progress until July, 1950, when he complained "that his head was falling apart". Soon he began to stagger. Urinary incontinence developed two weeks later and soon thereafter he lost all control of bowel function. When re-admitted to Children's Hospital on August 30, 1950, he held his head far to the right side, staggered towards the right side, and showed marked incoordination in using his hands.

On physical and neurological examination he was well developed and well nourished but appeared somewhat older than his stated age of four years. He seemed intelligent but extremely agitated, easily frightened and showed difficulty with speech. The blood pressure in the left leg was 108/60; the pulse was 104 and temperature 100. The general examination was entirely normal. The child reacted rather curiously to slight fear with facial grimaces and with body jerks without purposeful movement. The speech was explosive in type and gutteral sounds were evident. The gait was exceedingly ataxic with retropulsion towards the right side. The left eye was drawn inward and there was marked bilateral papilledema. Visual acuity showed marked loss bilaterally. The deep reflexes were not increased markedly although there was widespread torsion spasm in all muscles.

On September 9th, a pneumoencephalogram demonstrated a well outlined fourth ventricle and one-half centimeter of the inferior portion of the aqueduct of Sylvius. No air entered the ventricle beyond this point. Ten days later a ventriculogram showed a marked internal hydrocephalus with air in the third ventricle but no filling of the aqueduct of Sylvius could be demonstrated in spite of extensive maneuvering of the head with the child upside down. The spinal fluid examination was entirely within normal limits.

On September 19th, under general anesthesia, he was placed face down in the cerebellar head rest and a mid-line incision was made from the external occipital protuberance to the spinus process of C3. The arch of the atlas and the posterior portion of the

FIG. 1A

FIG. 1B

FIG. 1

occipital bone were removed. After the underlying cerebellar hemispheres were exposed, they were separated and the aqueduct of Sylvius was catheterized. The catheter passed one-half centimeter into the aqueduct where there was a firm mechanical block. Afterwards a burr hole was placed in the right occipital bone and a number ten soft rubber catheter inserted into the right lateral ventricle. The catheter was then brought out through the burr hole, underneath the scalp, and into the region of the posterior fossa where it was sutured into the cisterna magna. The wound was then closed.

The child made an unusually fine recovery and was discharged on November 23rd. Rehabilitation was delayed because of an inadequate home situation, and he spent three months at the Children's Convalescent Home. During six post-operative weeks he received 4,000 units of deep x-ray therapy to the mid-brain.

By February 17, 1951, he was walking well. The papilledema had disappeared and he had gained a considerable amount of weight.

The greatest circumference of his head is now 56.5 centimeters. He is left handed. He is in the second grade and continues to exhibit certain fear reactions. He has not had any illnesses since hospitalization five years ago (Figure 1).

An electroencephalogram shows a continuous dominant high voltage, twenty to twenty-two per second, fast pattern in the frontal regions bilaterally. Paroxysmal, high voltage, six per second slow waves, occurring in bursts lasting one to three

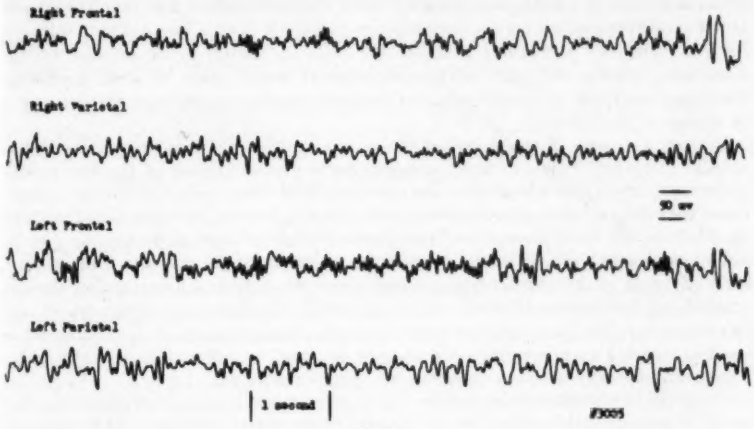

FIG. 2

seconds, are also evident on five or six occasions during an hour's tracing. High voltage spikes are seen from the right side and these are mixed with random high voltage slow waves and appear equally represented in the right frontal and right parietal area (Figure 2).

A complete psychometric evaluation was done by Dr. Emma M. Layman on March 3, 1955. The results of the Stanford-Binet, form M, indicate that his mental age is seven years and four months and his I.Q. eighty-eight. The summary of the results are listed as follows:

"Billy is a well built handsome boy with brown eyes and brown hair. He was friendly with the examiner and approached the examination situation with interest and enthusiasm. He showed no signs of apprehension and put forth excellent effort. Billy is left handed and somewhat awkward in the use of his hands. His voice is rather loud and high pitched. His articulation is good but he experiences some difficulty in finding the right words.

"Billy's Stanford-Binet age of seven years and four months and I.Q. of eighty-eight classified him in the dull normal group in general intelligence. However, several of his failures were 'borderline' failures so that his actual functional level probably is within the low average range. He is average or better in verbal reasoning, vocabulary and arithmetical ability, but is below average in visuo-motor coordination as well as in visual perception of form and space. His span of attention is variable. He is easily distracted and there are some perseverations in his behavior.

"Billy has gained significantly since his initial examination in September of 1950, at which time he scored an I.Q. of sixty-five. At present he is functioning at a high dull normal to low average level. He has made excellent compensation in other areas so that despite the demonstrated handicaps he is able to function quite adequately in social and academic situations".

DISCUSSION

Aqueductal stenosis is a rare complication following encephalitis. When it occurs, successful surgical therapy may be employed. In the records at the Children's Hos-

pital, 375 cases of meningo-encephalitis have occurred over a five year period and aqueductal stenosis has been a complication in only 3 cases. This patient, followed for five years since operation, is functioning quite adequately in social and academic situations. Presumably the ventriculo-cisternal anastomosis is still operating. Torkelson has reported functioning anastomoses after 19 years without interim repair or change of the tubing.

A partial stenosis of the aqueduct occurs in the acute phase of meningitis and is usually transient. This explains the latent picture of dilatation of the ventricular system. At times, stenosis persists and occasionally it occurs many years later. Sometimes there is a relative obstruction so that there is internal hydrocephalus without papilledema. In these cases serial electroencephalographic changes usually can be found. For example, if abnormal electroencephalographic changes occur at increasingly frequent intervals following meningitis one must suspect a continuing organic process and further neurological study, including a pneumoencephalogram, should be carried out. One must preserve central nervous tissue because once the structures are lost there is no reparative process such as occurs in other tissues of the body. Thus, early therapy is the only acceptable form of treatment.

Progressive enlargement of the head may or may not occur, depending upon the age of the child. If the sutures are well fixed (which occurs between 14 to 20 months) then there is no appreciable enlargement of the head although serial x-ray examinations of the skull may show an increasing number of convolutional markings. However, this is not a recommended method of follow-up since these changes are the result of permanent alterations in cortical structure. If the head fails to increase then papilledema occurs. Papilledema is a latent sign of the disorder, and one should recognize the complication before papilledema is obvious.

Brain stem and cerebellar signs are frequently observed in stenosis of the aqueduct of Sylvius. Among some of the more specific neurological symptoms and signs are: (1) staggering gait, (2) retropulsion, (3) nystagmus, (4) diplopia, (5) weakness of both arms and legs, (6) loss of bowel and bladder control and (7) increasing headache. These signs following meningitis may also be permanent or transient residuals. On the other hand, these signs should not be progressive. Therefore, progression is the indication for a careful neurological survey.

The value in using deep x-ray therapy is controversial among neurological workers, but there is adequate data to suggest that it limits gliosis. It cannot be recommended in place of immediate surgical therapy for the period necessary to test its effectiveness is too long and further brain damage may occur in the interval.

SUMMARY AND CONCLUSIONS

This child who had a ventriculo-cisternal anostomosis for stenosis of the aqueduct of Sylvius 5 years ago, is now physically normal and enjoys adequate function in social and academic situations. The follow-up period of 5 years permits one to comment on the validity of the surgical procedure employed in this patient. The diagnosis of aqueductal stenosis cannot be made without a combined pneumoencephalographic and ventriculographic study. However, serial electroencephalogram changes following an intracranial inflammation may prove useful in detecting the presence of a progressive destructive intracranial process. Since most of the clinical signs are referable to the brain stem and cerebellum they usually antedate the electroencephalographic changes. It is therefore clear that progressive neurological disturbances are more important and when present the child should have a careful neurological survey to find the responsible lesion. Waiting too long results in irreversible losses of vital nervous tissue.

TUBERCULOUS EPIDIDYMITIS

Paul B. Bender, M.D.
George J. Cohen, M.D.

Because tuberculous epididymitis is a relatively rare entity, especially in children, the following case is presented.

Case Report

L. T., a two year old colored male was admitted to Children's Hospital on February 25, 1955 because of swelling of the left scrotum for one month.

Review of the present illness revealed that the child was first seen in our Out Patient Department on January 23, 1955 with a painful, tender, firm, nonreduceable mass 1.5 x 3.5 cm. in diameter in the left scrotum. He was referred to surgical clinic, but the next day was admitted to another hospital where the same history and physical findings were noted. A tuberculin patch test at that time was negative as were urinalysis and serology for syphilis. After treatment there with penicillin and ice bags, there was no improvement; therefore on January 30, 1955 the scrotal sac was explored. The gross appearance of the testis was consistent with the diagnosis of orchitis, and a biopsy specimen was taken. This was reported as showing chronic granulomatous tissue suggestive of tuberculosis, but no acid-fast-staining organisms were seen. Following an uneventful postoperative course he was discharged on February 5th.

On admission here physical examination was normal except for medium sized nodes in the cervical and inguinal areas. There was a 0.5 cm. dry ulceration on the left scrotum, adherent to and overlying a hard, tender, indurated, slightly warm 1.5 x 3 cm. mass. Rectal examination revealed no involvement of the prostate. Admission urinalysis was normal as were all subsequent urinalyses. Hemogram on admission showed 7,400 leukocytes with 19 per cent segmented neutrophiles, 70 per cent lymphocytes and 11 per cent monocytes. The leukocytes never exceeded 11,300 and there was always a predominance of lymphocytes. On admission the sedimentation rate was 16 mm/hr (Wintrobe). Chest x-ray on admission showed an infiltration in the right apex. PPD #1 read on February 28, 1955 at 48 hours was strongly positive. Three successive gastric washings, two successive 12 hour urine specimens, and material from the scrotal ulcer all showed no growth on culture media for tuberculous organisms after 8 weeks incubation. Routine culture of material from the scrotal ulcer grew out diptheroids and micrococci. A course of penicillin and aureomycin was begun on March 1, 1955 in an effort to eradicate secondary infection of the scrotum, and to see whether there would be any change in the chest x-ray. After 2 days the scrotal mass was less tender but remained enlarged. After 10 days of penicillin and aureomycin, the chest x-ray showed no change. Because the consensus at that time was that the patient probably had a progressive primary tuberculous process, antibiotics were discontinued, and isoniazid (25 mg. three times a day) was begun on March 10th. On March 14th para-amino-salicylic acid (.5 grams four times daily) was begun. A sedimentation rate on March 7th was 23 mm/hr, and on March 21st was 17 mm/hr at which time the chest x-ray showed some resolution of the apical lesion.

Because the swelling in the left scrotum remained hard, nontender, and virtually the same size, it was felt to be tuberculous. On March 30th a left epididymo-orchiectomy was performed. The tissue grossly showed many soft yellowish areas. On microscopic section there was granulomatous inflammation of the testis and epididymis and caseation necrosis of the epididymis consistent with tuberculosis. (Fig. 1) Both

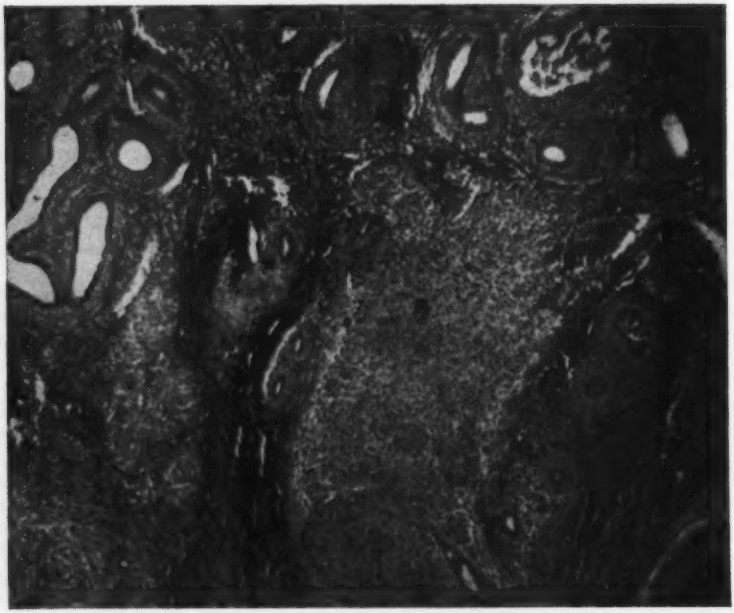

FIG. 1. Section of Epididymis showing granulomatous reaction and giant cell

acid fast and fungus stains of the tissues were negative. Unfortunately, no material was inoculated into tuberculosis media.

Immediately after surgery streptomycin 1.0 gm daily was added to his therapeutic regime. After one week, the dosage was reduced to 1.0 gm of streptomycin three times weekly. The scrotal wound healed promptly and without complication. On April 4th, the sedimentation rate was 10 mm/hr and the chest x-ray showed further resolution of the right apical lesion.

Throughout his hospital course the patient was afebrile, cheerful and without any general symptoms. On April 25th, he was transferred improved, to Glenn Dale Sanitorium for convalescence and further therapy.

DISCUSSION

Paul B. Bender, M.D.

Mycobacterium tuberculosis has no respect for age, sex, race, or climate. It has no respect for any vital organ. It is a relentless enemy to the last, and must be attacked with great vigor if the offending pathology is to be annihilated.

Tuberculous epididymitis is always a secondary infection with the primary site almost always being pulmonary. Most cases of genital tuberculosis, whether in children or in adults, are secondary to renal tuberculosis. However, many urologists contend that the first genito-urinary organ to be involved is the epididymis. This contention is based on the relative infrequency of palpable tuberculous prostatitis and seminal vesiculitis and the absence of abnormal urinary findings in a considerable number of such cases.

The apparent rarity of the lesion in children is largely due to failure to recognize the condition. The early progress of the disease is often masked by a hydrocele, and the true nature of the lesion is not recognized until gross evidence of prostatic involvement, resistant pyuria or scrotal fistula occur. Even so, the overall incidence in the pediatric age is not high.

The pathogenesis of tuberculous epididymitis is either directly by the hematogenous route, or more commonly a descending infection from the prostate and seminal vesicles with the organism migrating down the vas deferens or its accompanying lymphatics to the epididymis. Prostato-vesicular lesions are almost always secondary to renal tuberculosis.

The initial involvement in the epididymis is usually in the tail or globus minor, then to the remainder of the organ and to the testicle. Sometimes the vas deferens will be thickened, indurated and beaded. Extension to the other epididymis occurs in the majority of untreated cases and usually within six to eight months. Secondary scotal fistulas are likely to occur if the tuberculous epididymitis progresses to suppuration.

Histologically the lesion may be predominantly caseous, sclerotic or a combination of both.

The local lesion may be either acute or chronic in nature. The acute variety simulates acute non-specific or gonorrheal epididymitis with the gland enlarged, hard, smooth and very tender. It is frequently impossible to differentiate the epididymis and testis in the acute inflammatory mass.

The chronic variety may appear as a continuation of the acute process, or develop gradually with a painless or slightly tender nodular swelling of the epididymis. Spontaneous, complete healing rarely occurs in either the acute or chronic forms.

The establishment of the correct diagnosis is paramount. Acute tuberculous epididymitis cannot be differentiated with certainty from the other varieties of acute epididymitis. A waiting period up to ten weeks is permissible to allow regression of the acute inflammatory process. During this interlude one of the chemotherapeutic agents or antibiotics, not effective in tuberculosis, may be administered just in case the infection is not tuberculous in nature. Once the acute inflammation subsides, the irregular nodular tuberculous epididymis then becomes palpable unless a tense hydrocele is also present. Aspiration of the hydrocele is justifiable as an aid to diagnosis.

In chronic tuberculous epididymitis there may be no symptoms other than the presence of a painless or slightly tender nodular swelling in the scrotum, or the appearance of a hydrocele. The epididymis is readily distinguished from the testis while involvement of the latter is manifested by a smooth enlargement. Fever is absent or low grade. Inguinal lymphadenopathy is not a part of the picture as the lymphatics traversing the spermatic cord empty into the deep iliac para-aortic and peri-renal nodes.

Intrascrotal lesions which must be differentiated include tumor, gumma, non-tuberculous epididymitis and certain fungus diseases.

The prognosis depends on the extent of active tuberculosis elsewhere, especially pulmonary or renal. The development of tuberculous epididymitis rather than miliary tuberculosis is in itself an indication of good inherent resistance to the disease. The removal of the tuberculous genital lesion together with adequate medical management affords a good prognosis providing the primary lesion is not extensive.

Genital tuberculosis should be treated like tuberculosis elsewhere in the body, with sanatorium care or its equivalent giving the best possible chance of cure. Streptomycin is administered intramuscularly in 0.25 to 1.0 gm. doses, three times weekly. Para-aminosalicylic acid is given orally up to 12 gms. daily in divided doses for the adolescent and reduced in proportion to the weight in younger children. It is neces-

sary to crush the tablets and give with feeding in children. Isoniazid is administered orally in dosage of 5 to 10 mgm. per kilogram of body weight daily in three divided doses. General nutrition and rest must never be overlooked.

In reference to the patient in question all clinical, laboratory and pathological findings favor strongly a diagnosis of tuberculosis. The only missing link is the actual visualization of at least one or two tubercule bacilli. Even so the appearance of a strongly positive PPD skin test within a period of one month, the presence of an apical pulmonary lesion, the failure of the biopsy incision to heal, and the hard, irregular, slightly tender epididymis firmly fused to the testis, all afford a presumptive preoperative diagnosis of tuberculous epididymitis. In cases of acute epididymitis in which tuberculosis is present elsewhere in the body, genital tuberculosis is present in over 90 per cent of such cases. The biopsy specimen manifested a chronic granulomatous reaction suggestive of tuberculosis while the surgical specimen showed definite caseation necrosis.

The demonstration of acid fast bacilli in tissue sections is a formidable job in many instances. Serial sections, infinite patience and many hours of work and observation are frequently required to visualize the mycobacterium.

The normal urinary findings together with negative urine culture for tuberculosis suggest that the kidneys are not involved in the activity of the disease although it is quite probable that a transitory tuberculous bacilluria occurred sometime during the course of the disease.

TUBEROUS SCLEROSIS

J. William Oberman, M.D.
John F. Regan

Tuberous sclerosis (epiloia, Bourneville—Pringle disease) is a rare condition classically represented by the triad of epilepsy, mental retardation and adenoma sebaceum. It is probably congenital, may be hereditary or familial, and may have its onset in infancy or not until adolescence. The pathological abnormality consists of multiple developmental anomalies in tissues of ectodermal origin, primarily manifested by tumor formation in the cerebrum together with the frequent occurrence of tumors in almost every other organ of the body.

Case Report

G. W., an eight year old white male, was admitted to Georgetown University Hospital on May 27, 1954 for extreme lethargy following a grand mal convulsion the day prior to admission. The history was obtained that he had been having grand mal and petit mal seizures since five months of age, initially two or three times weekly. He was hospitalized at the age of two years at Children's Hospital for evaluation of his convulsive disorder. Spinal tap at that time was normal. An electroencephalogram was reported as diffusely abnormal and a pneumoencephalogram was within normal limits. Dilantin and phenobarbital were prescribed and the patient was discharged with a diagnosis of cerebrocerebellar ataxia with major convulsions. At home he

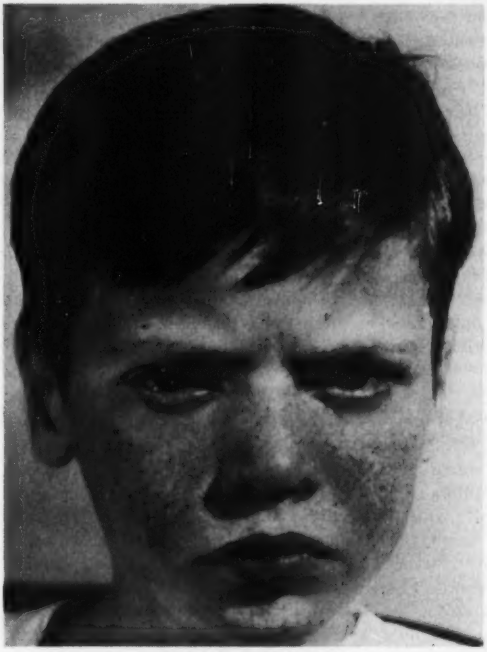

FIG. 1. Adenoma sebaceum

continued to have both grand mal and petit mal seizures three or four times weekly and was re-admitted to Children's Hospital at the age of three and one half years when a right carotid-jugular anastomosis was performed. No particular improvement was noted and he continued to have frequent convulsions. He had been observed regularly in the neurological clinic over the intervening years but the convulsions had never been completely controlled. Therapy just prior to admission consisted of mysoline, mebaral and phenobarbital. Despite these medications, seizures had been increasing in severity and were occurring almost daily.

He was the product of a full-term, uncomplicated pregnancy. Labor lasted four hours and delivery was uneventful. Birth weight was eight pounds, nine ounces. Early growth and development had been normal. He talked at twelve months of age and walked at eighteen months. Toilet training was complete at eighteen months. Four years prior to admission a papular rash had been noted across the bridge of the nose and on both cheeks. This rash was exacerbated by sunlight and resisted all attempts at therapy. For several years prior to admission he had become increasingly more irritable and was extremely negativistic and uncooperative. He was currently attending the second grade in school but was not progressing well and special classes had been recommended by his teachers.

The patient was the third of five children, the remainder of whom were living and well. Father and mother were in good health and there was no family history of neurological or mental disease.

On admission the patient was extremely lethargic. He was observed overnight and gradually roused from his lethargy. Physical examination at this time revealed bilateral horizontal nystagmus, an erythematous papular rash with a butterfly distribution over the malar eminences (Figure 1) and a few cafe au lait spots on his chest and abdomen. Neurological examination except for the nystagmus was completely normal. Ophthalmoscopic examination was normal. While hospitalized he was noted to be extremely uncooperative and suspicious. His mood vacillated between friendliness and complete withdrawal. He was very fearful of being sent to the operating room for not doing what the nurses had told him to do.

X-rays of the skull were normal. Spinal fluid pressure was 370 mm. but was otherwise normal. An electroencephalogram was reported as diffusely abnormal. A pneumoencephalogram failed to outline the ventricular system but air was present over the cortical surfaces. Dermatological consultation confirmed the diagnosis of adenoma sebaceum. The patient had no further convulsions in the hospital and was discharged on June 2, 1954 to be followed in the neurological clinic.

DISCUSSION

The exact etiology of tuberous sclerosis remains obscure but increasing evidence suggests that it is a developmental anomaly commencing early in fetal life. The cells of the cerebral tumors are thought to arise from the neural tube and the cells of the extracerebral tumors from neural crest cells. The disease occurs most commonly in Europe, especially Great Britain. It is occasionally familial, the occurrence in two or more siblings having been reported. Frequently, a careful family history, while failing to discover further classical instances of this disease, detects abortive forms in siblings or parents. There is an increased familial incidence of mental retardation, epilepsy with a strong psychopathic taint, kidney tumors, adenoma sebaceum and cafe au lait spots. Adenoma sebaceum or epilepsy or both may occur without mental defect.

Tuberous sclerosis is thought to be closely related to von Recklinghausen's disease (neurofibromatosis) since both diseases have as part of their clinical picture cafe au lait spots, fibromatoma and nevi. Both are hereditofamilial disorders which are often associated with psychopathic trends. Identically appearing retinal tumors may be noted in both diseases. Epilepsy has also been known to occur in von Recklinghausen's disease although it is a much rarer phenomenon.

Characteristically the gross appearance of tuberous sclerosis is that of sclerotic tumor masses in the cortex of the cerebral hemispheres. There may be from one to thirty of these whitish nodules, each measuring almost 2–3 centimeters in diameter and located at the summit of a gyrus or extending over one or more convolutions. The tumors have a firm consistency like that of rubber or a raw potato, thus the name tuberous sclerosis. Occasionally, the tumor-like masses will protrude into the ventricular system but they occur in any other portion of the central nervous system. Histologically these tumors are composed of an overgrowth of glial fibers and in addition contain large cells which may be abnormal ganglion cells.

Additional tumors are frequently present in other organs. One of the most frequent is rhabdomyoma of the heart; these are usually small and multiple and rarely cause symptoms. Renal tumors are said to be present in eighty per cent of cases but are rarely diagnosed during life. These are multiple, bilateral, of varying size and are nearly always cortical. They seldom metastasize. Such tumors are usually of an embryonal mixed type and may vary from an angiosarcoma to hypernephroma. In the lungs the alveoli and bronchioles are transformed into small cavities, and areas of

interstitial myofibrosis producing a miliary, granular appearance. Other frequent sites of tumor formation include duodenum, retina, thyroid, thymus, adrenal gland and liver. Occasionally these visceral tumors give rise to the presenting symptoms.

Adenoma sebaceum is frequently present on the face. Associated skin lesions include small flat fibromas, cafe au lait patches, nevi, papillomas, the shagreen patch and hypertrichosis.

Clinically, in the classical case signs and symptoms appear in infancy and early childhood. These children are frequently slow to develop with the result of a delay in sitting, crawling, speaking and walking. Mental retardation when present is usually observed by the third year of life but the degree varies widely from case to case. The children are frequently apathetic, excitable and negativistic, and often assume bizarre positions and perform stereotyped movements. There is believed to be a strong familial psychopathic trait combining an intellectual defect and a primitive type of catatonic schizophrenia.

Epileptic seizures usually appear during the first two years of life and may be grand mal, petit mal, Jacksonian, or psychomotor in type. Seizures number from once a year to ten per day. There may be long periods of remission regardless of therapy. Mental deterioration is progressive and terminally the number of convulsions may greatly increase. The neurological examination is usually normal. Occasionally single large tumors may give rise to symptoms suggestive of brain tumor.

Adenoma sebaceum is usually present by the fourth or fifth year and consists of a red papular rash over the nose and cheeks in a "butterfly" distribution. This rash is usually asymptomatic and resistant to therapy. Some investigators believe that the diagnosis of tuberous sclerosis cannot be made in the absence of adenoma sebaceum except in those members of a family of a patient with tuberous sclerosis who show neurologic or psychiatric anomalies. After eruption of the permanent teeth the rash frequently coalesces and darkens to a deep red or brown hue. Other cutaneous manifestations have been previously mentioned. The shagreen patch is an uneven thickening of an irregular area of skin usually located in the lumbosacral region; it is the color of adjoining skin.

Rarely the cutaneous lesions do not put in an appearance until puberty or adulthood.

A characteristic retinal lesion is frequently observed opthalmoscopically. This is the phakoma which is a flat, white, round or oval area about one-half the size of the optic disc. Other frequently associated congenital anomalies include hare lip, high palate, myopia, spina bifida, polydactylism and congenital heart disease.

X-rays of the skull may demonstrate calcification of the subependymal tumors. Ventriculography may reveal evidence of tumors projecting into the ventricles or merely a dilated ventricular system. X-ray of the chest may reveal miliary lesions or recurrent pneumothorax as a result of rupture of one of the small cystic lesions.

The ultimate prognosis depends on the extent of the syndrome. In the classical case the course is rapidly downhill; most deaths occur between the ages of five to fifteen years. However, some patients may live to thirty or forty years of age. The usual causes of death are cachexia, pulmonary infection and status epilepticus. Prior to their death many of these children may be institutionalized because of mental deterioration and emotional outbursts. A rare cause of death is increased intracranial pressure. In the incomplete syndrome the patient has no neuropsychiatric symptoms and may have an entirely normal life, the only presenting complaint being adenoma sebaceum. The therapy of tuberous sclerosis is purely symptomatic and is directed primarily toward controlling the convulsions.

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EDITORIALS

ACCIDENT PREVENTION AND POISON CONTROL

In recent years the physician's ability to limit the infectious diseases, which formerly produced most of the mortality and morbidity of childhood has emphasized the prominence of other fields in the statistics of childhood illness. Among the most important of these other fields is that of accidents, which are at present the leading cause of death among children between one and fourteen years of age.

In connection with this awareness of the accident problem a national program aimed at prevention of home accidents and particularly the accidental ingestion of poisons in the home, has been undertaken through the auspices of the American Academy of Pediatrics. On July 15, 1954, an accident prevention program, beginning with a method for control of household poisonings was initiated in the District of Columbia Metropolitan area. Seventeen hospital emergency rooms agreed to report all cases of accidental ingestion of household substances coming to their attention. At the same time a central bureau for the dissemination of technical information concerning accidental poisoning was established at the Children's Hospital. This bureau includes a 24-hour telephone information service, a gradually growing library of technical data on poisons and poison control methods, and the evolution of statistical summaries on the magnitude of the local poisoning problem.

During the six month period from July 15, 1954 to January 15, 1955, the poison control center received 212 reports of accidental poisonings from the cooperating hospitals. A wide variety of substances was involved. Sixty-nine of the 212 cases required hospitalization but there were no deaths. A detailed breakdown of the statistics for these 212 cases is appended. Critical examination of these figures shows that the incidence of accidental ingestion of household preparations depends, in the main, upon their availability to the child. Thus, in the way of medications, aspirin, laxatives, sedatives, and other medications commonly present in the house,

such as liniments, cosmetics and antiseptics are involved. Such other household substances as laundry bleach, lye, kerosene, turpentine, and rodenticides, insecticides, pesticides, are common causes of trouble.

In a recent review of the death certificate figures for accidental poisoning on a national level, Dr. Katherine Bain of the U. S. Children's Bureau estimated that the majority of the lives lost could have been saved were aspirin, sedatives, lye, kerosene, and turpentine not available to the children who were poisoned by them. With this we would heartily agree, since our figures, although containing no mortality, certainly show that the morbidity was mainly due to very common, easily available household substances.

Every physician dealing with children should make the poison control and accident control program a part of his professional activities. Parental education in the methods of preventing accidents in the home and particularly, in the proper storage, and proper safeguarding of poisonous household substances, would go a long way toward reducing the magnitude of this problem among children.

ALLAN B. COLEMAN, M.D.

Chairman, Committee on Accident Prevention, District of Columbia Chapter, American Academy of Pediatrics and Director, Washington Metropolitan Area Poison Control Center

Editor's Note: Please turn to the next page for table showing distribution of household substances ingested and frequency of ingestions requiring hospitalization.

HOUSEHOLD SUBSTANCES SWALLOWED AND HOSPITALIZATION
Washington, D. C.—July 15, 1954 through January 15, 1955

Substance Swallowed		All Cases	Cases Hospitalized
I. *Medications*		*110* (52%)	*26* (38%)
A. *Internal*	*97* (46%)		*22* (32%)
1) Aspirin	50		
2) Laxative	4		
3) Sedative	23		
4) Other	20		
B. *External*	*13* (6%)		*4* (6%)
1) Liniment	2		
2) Cosmetics	2		
3) Antiseptics	4		
4) Other	5		
II. *Cleaning, polishing, and sanitizing agents*		*32* (15%)	*15* (23%)
1) Bleach	10		
2) Lye	4		
3) Polish	6		
4) Paint	1		
5) Lysol	6		
6) Other	5		
III. *Petroleum distillates (kerosene, gasoline, etc.)*		*25* (11%)	*15* (22%)
IV. *Pesticides*		*26* (12%)	*9* (13%)
A. Rodenticides	*11*		
B. Insecticides	*14*		
C. Other	*1*		
V. *Turpentine*		*8* (4%)	*3* (4%)
VI. *Other*		*8* (4%)	
VII. *Unknown*		*1* (.5%)	
VIII. *Multiple poisoning*		*2* (.9%)	
Grand total		*212* (100%)	*69* (100%)

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